Scientific Abstract

It is estimated that prostate cancer will be the leading male cancer diagnosis and the second most common cause of male cancer death in the United States in 2000. Prostate cancer detected in early stages can be treated successfully by surgery or radiation. However, 10-15% of subjects will have metastatic cancer at the time of diagnosis. Of subjects undergoing radical prostatectomy, approximately 20-30% will have positive margins or capsular penetration at the time of their resection. Thus, a significant number of subjects are at risk for post-surgical local recurrence. In other patients, metastatic prostate cancer will subsequently develop after some form of definitive initial therapy (either surgery or radiation). The most common anatomical locations for metastatic disease are bone and lymph nodes. Androgen ablation can delay progression, but no effective therapy is available for patients and the need for new therapeutic approaches to treat advanced prostate cancer is clear. Progression to bone is a common feature in these patients and is the major cause of morbidity and mortality. Androgen-independent prostate cancer bone metastasis is a clear unmet medical need.

Direct introduction of therapeutic genes into malignant cells *in vivo* may provide effective treatment of solid tumors such as adenocarcinoma of the prostate. The proposed study will use the adenoviral vector Ad-mOC-E1a (OCaP1), which contains a murine osteocalcin (OC) promoter to regulate the production of the adenoviral E1a protein to allow for restricted viral replication and subsequent lysis of tumor cells. The OC promoter is developmentally regulated, with peak expression in the neonate. It functions primarily in osteoblasts found in growing bone. Additionally, it has the ability to drive gene expression in tumors that can undergo ossification, including prostate cancer.

A majority of prostate cancer metastatic lesions demonstrate an osteoblastic phenotype and prostate cancer cell lines have been shown to express high levels of thymidine kinase (TK) activity after infection with a replication-deficient adenovirus containing hsv-TK regulated by a murine OC promoter (Ad-OC-TK). Several non-prostate cancer cells and normal cells examined failed to demonstrate TK activity after infection with Ad-OC-TK. When cell lines and animals containing human prostate cancer are infected with Ad-OC-TK and exposed to ACV, there is a marked diminution in tumor growth, both *in vitro* and *in vivo*. These results led to a phase I study with Ad-OC-TK (OBA #9812-276). The safety results of this study reinforced the preclinical results in that Ad-OC-TK was well tolerated and there was evidence of tumor-specific TK expression, but not extra-tumoral TK expression. Hence the OC promoter limited the transgene expression to tumors. Additionally, biological evidence of anti-tumor effects in the presence of Valacyclovir were observed.

This protocol is a phase I investigational study of intralesional injections of Ad-OC-E1a for the treatment of metastatic or recurrent prostate cancer. Initially, one index lesion (local recurrence or metastasis) will receive one injection of 1×10^{10}, 1×10^{11}, 1×10^{12}, or 5×10^{12} viral particles of Ad-mOC-E1a. This will be followed by an escalation of the number of index lesions treated (2-5) in a different group of subjects, in order to maximize the delivery and to assess the therapeutic effect.

The primary objective of this study is to demonstrate the safety of one intralesional injection of Ad-mOC-E1a into one to five index lesions. The secondary objectives are to determine the maximum tolerated dose, monitor tumor responses, and evaluate time to progression. Clinical, serologic, tissue, and radiologic evaluations will also be performed to confirm the biologic feasibility and the potential efficacy of this approach.